REMARKS/ARGUMENTS

Claims 33, 56-59, 61 and 63-152 are pending, claims 129-152 having been added. New dependent claims 129-131, 132-134, 135-137, 138-140, 141-143, 144,145, 147-149, 150-152 are directed to one of the three antibodies types recited by independent claims 61, 68, 80, 86, 98, 104, 116, 122, respectively. Thus, new claims 129-152 add no new matter.

All pending claims stand rejected for alleged lack of enablement of the claims under 35 U.S.C. § 112, first paragraph. The Examiner reiterates her opinion that the overall field of gene therapy was unpredictable at the priority date of the application. The Examiner alleges it is unpredictable which antibodies within Aβ1-10 have the desired activity in that of the tested antibodies only 10D5 had activity and 2H3 was discontinued because of rapid clearance. The Examiner faults the application for alleged lack of specific guidance as to vectors, promoters, routes of vector administration or nucleic acid sequences encoding antibodies. The Examiner discounts the Koller declaration on the basis that the immunization generated polyclonal antibodies which are not analogous to monoclonal antibodies, and because of differences between administration of a protein to generate antibodies and generating antibodies by administering a nucleic acid. The Examiner then repeats her previous remarks about the Arafat reference. Applicant maintains traverse.

Although the Examiner acknowledges applicant's position that the claimed methods represent an undemanding form of gene therapy which require only transient accumulation of antibody in the blood, the Examiner continues to take the view that one cannot predict the success of the methods based on unpredictability in the field of gene therapy as a whole. In fact, the claimed methods present different issues from the field of gene therapy as a whole, and their success can be reasonably predicted. First, many aspects of the claimed methods can and have been tested by the direct delivery of monoclonal antibodies. Thus, information such as an appropriate specificity of antibodies, and knowledge that peripherally administered antibodies can cross the blood brain barrier in sufficient proportions to achieve activity has already been obtained. Given the demonstrated activity of antibodies directly delivered to the blood, it is not difficult to predict similar activity of antibodies delivered to the

blood via expression. Second, expressing a protein in blood is much simpler than targeting expression to a specific tissue. The relative simplicity of merely accumulating a protein in the blood versus expressing a vector in a specific cell type versus is noted by the Verma reference cited by the Examiner (*see* p. 239, column 1, third paragraph). The reference points out that protein accumulates in the blood from expression in a number of different cell types including muscle, liver cells, fibroblasts and blood cells themselves. Also, the accumulation of a protein in the blood allows for easy assessment of its levels, and consequent adjustment of dosage and/or frequency of administration to suitable levels. Thus, treating diseases by accumulation of a protein in the blood is viewed as being relatively simple: "to correct blood-clotting disorders, such as hemophilia, ***all that is needed*** is a therapeutic level of clotting protein in the plasma" (p. 239, first column, third paragraph, emphasis supplied).

The Examiner's contention that even direct delivery of a monoclonal antibody having an epitope within Aβ1-10 is unduly unpredictable is incorrect. The Examiner's view is based on 10D5 being the only example of a monoclonal tested in the specification to show efficacy. However, the other monoclonals tested, except for 2H3, had an epitope specificity outside Aβ1-10. 2H3 antibody was discontinued not because it had the wrong epitope specificity but because it was cleared too rapidly *in vivo* (*see* page 70 of the instant specification). Even if it assumed *arguendo* that antibodies having epitopes outside Aβ1-10 were not demonstrated to have statistically significant activity, this does not mean that other antibodies having epitopes within Aβ1-10 are not effective. Several other antibodies within Aβ1-10 that are effective with statistical significance are disclosed by Bard et al, PNAS 100, 2023-2028 (2003) (subsequent work from a group including the present inventor), submitted herewith. Thus, statistically significant activity can be obtained from a number of antibodies with epitopes with Aβ1-10. Insofar as some antibodies having epitopes within Aβ1-10 lack such activity, it would be a simple matter to exclude them, as 2H3 was excluded, by first screening them by direct administration in the mouse model disclosed in the examples of the specification.

The Examiner faults the specification for providing lack of guidance as to vectors, promoters, routes of administration and nucleic acids encoding antibodies. With respect to vectors and promoters, the art was sufficiently advanced at the relevant date to provide suitable

vectors and promoters. For example, deleting the E1 gene from adenoviral vectors was common practice in the art before the priority date of the application (*see e.g.*, Eck at p. 86, second column, second paragraph, Verma at p. 241, first column second paragraph). A specification need not disclose and preferably omits what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1984).

With respect to the route of delivery, the presently claimed methods can treat amyloid pathology in the brain by delivery of antibody to the blood. As Verma makes clear, delivery to the blood can be achieved directly or indirectly. Direct delivery can be achieved by expressing a protein in the blood. Indirect delivery can be achieved by expressing the protein in other tissues, including muscle, liver cells, and fibroblasts, from which expressed protein is delivered into the blood. Thus, it is appropriate that the claims not be limited to any particular site of the delivery.

With respect to disclosing the sequences of nucleic acids encoding antibodies, it is noted that the hybridoma producing 10D5 has been deposited. No difficulty is apparent in determining the nucleic acid sequence of an antibody from a deposited hybridoma. It would also be a routine matter to produce other antibodies with epitope specificities with Aβ1-10 and similarly determine their nucleic acids.

The Koller declaration was previously submitted for two purposes. First, it demonstrates that only relatively brief treatment was effective to achieve a statistically significant benefit (*see* paragraph (2) stating the results were obtained from an exploratory phase I trial). Second, this benefit was achieved not withstanding considerable variation in antibody response between different individuals (*see* declaration at paragraph (6)). The Examiner discounts this declaration for two reasons. First, the Examiner alleges that the Koller declaration relates to generation of polyclonal antibodies, whereas the presently claimed methods generate monoclonal antibodies. However, the nexus between polyclonal antibodies and monoclonal antibodies is shown by other data in the specification. That is, the application shows that both polyclonal antibodies and the monoclonal antibody 10D5 achieve statistically significant activity. Similar results have been shown for other monoclonals having epitopes within Aβ1-10. Thus, activity obtained for polyclonal sera is reasonably predictive of activity of monoclonals

having epitopes within Aβ1-10. Second, the Examiner discounts the Koller declaration now as before in that it relates to administration of a peptide rather than a nucleic acid. However, there is a nexus between administration of a peptide and administration of a nucleic acid because the result in both cases is the production of antibody. Thus, the conclusion from the Koller declaration that useful therapeutic activity can be obtained notwithstanding transient presence and variable levels of antibody is relevant to the claimed methods.

The Examiner then turns to the Arafat reference and repeats her remarks from the previous office action without addressing applicant's response. Thus, applicant reiterates his previous remarks here.

First, the Examiner criticizes the submission of Arafat as inadequate to show enablement in that Arafat was published four years after the priority date of the present application. However, that enablement is determined from the specification as filed does not preclude the applicant from providing evidence after the filing date which demonstrates that the claimed invention works (*see* MPEP § 2164.05). Here, Arafat was cited to show that recombinantly expressed antibody can properly fold. As noted in the previous response, it also shows the feasibility of using the CMV promoter disclosed by the present specification for accumulating antibody in the blood.

Second, the Examiner finds fault in that the adenoviral vector used by Arafat was deficient in the E1 gene. However, the Examiner does not address the fact that it was common practice to delete E1 and other genes from adenoviral vectors well before the priority date of the invention as discussed above (*see e.g.*, Eck at p. 86, second column, second paragraph, Verma at p. 241, first column second paragraph).

Third, the Examiner alleges that Arafat's work differs from the claimed methods in that Arafat discloses an antibody that recognizes an antigen present on tumor cells and not in the brain. Although the ultimate pathologies being treated are different in Arafat and the present application (a tumor vs. amyloid deposits in the brain), the route of delivery can be the same. Both approaches can be effected by delivery of antibody to the blood, and Arafat shows the feasibility of achieving this.

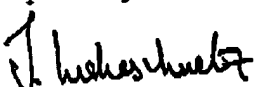
Fourth, the Examiner alleges that Arafat's teaching is confined to single-chain antibodies. Although Arafat chose to express single-chain antibodies, there is no reason to expect that double-chain antibodies would not properly fold in a variety of cell types present in a patient. Antibodies have been successfully produced in a diverse cell types including mammalian cell cultures, transgenic animals, bacteria, plant cell cultures, transgenic plants and insect cells (*see* Schillberg, *Cell. Mol. Life Sci.* 60, 443-45 (2003) and Guttieri, *J. Immunol. Methods*, 246, 97-108 (2000) of record). Many of these cell types do not naturally express antibodies. Schillberg notes that full size antibodies and a variety of derivatives can be produced, and that all of these forms were successfully expressed even in plant cells (see pp. 434 and 436). Given that double chain antibodies can successfully fold even in insect cells and plant cells, there is no reason to expect otherwise in a variety of cell types in a patient, and particularly in the blood cells of a patient that naturally express antibodies.

The Office Action concludes by listing the *Wands* factors, and stating that an analysis of them leads to a conclusion that the claims lack enablement. However, the analysis did not take into account the nature of the invention, in particular that it merely requires a transient expression of a protein in blood to have some activity. The analysis also did not take into account several relevant facts regarding the state of the prior art; including for example, the common practice of omitting an E1 gene from adenoviral vectors. Likewise, the analysis did not take into account the fact that antibody expression and folding had been demonstrated in a variety of cell types. The analysis also disregards the working examples and Koller declaration. Although it is acknowledged that these do not involve administration of nucleic acids, they do provide evidence from which success of the claimed methods can reasonably be predicted, as discussed above. The office action also takes an unduly pessimistic view of the unpredictability of gene therapy as a whole given the number of gene therapy trials in progress, the number of patents that have issued in this field already, and the fact that the standard for patentability is considerably lower than that for FDA approval and does not require that a system be "entirely satisfactory," free from side effects or to have demonstrated clinical efficacy, as discussed in the previous response. When the Wands factors are considered in light of all relevant information, it is respectfully submitted that they do not compel a finding of undue experimentation.

Claims 105, 106, 108, 123-124, and 126 stand rejected under 35 U.S.C. § 112, second paragraph for alleged lack of antecedent basis. In response, claims 105, 123, 106 and 124 have been amended to delete the definite article "the." Claims 108 and 126 have been amended to provide antecedent basis for "multiple occasions."

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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